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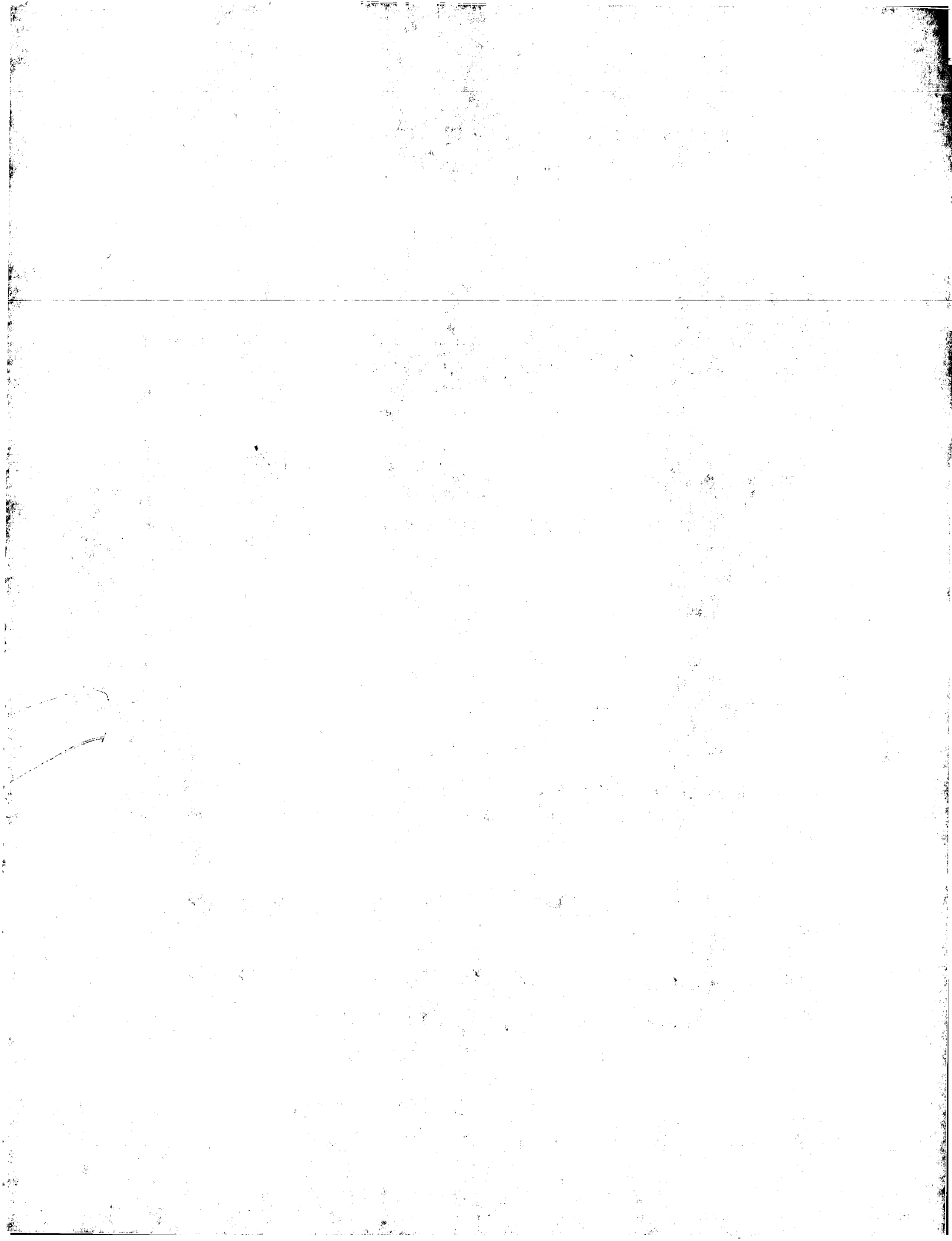
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**ANTIPRURITIC DRUG AND ANTIPRURITIC COMPOSITION.**



An antipruritic drug comprising a zinc-amino acid conjugate and an antipruritic composition containing  $2.6 \times 10^{-3}$  to  $2.6 \times 10^{-1}$  M of said drug.

## TECHNICAL FIELD

The present invention relates to an antipruritic agent and an antipruritic compound, and more specifically, it relates to an antipruritic agent and an antipruritic compound, in which zinc is the main ingredient.

## BACKGROUND ART

The skin possesses the function of protecting the body from various forms of stress due to the external environment, but if this body maintenance function becomes unbalanced, various forms of skin conditions appear, such as chapped skin and scabies.

As the majority of these skin conditions are accompanied by itching, this itching leads to skin pruritis, which can frequently exacerbate the original skin condition.

There are individual differences in the degree of itching in such cases of pruritic skin diseases and cases of skin pruritis, ranging from that which is extremely mild to that which is extremely severe. In addition, as a sebum deficiency, which is one cause of pruritis, is observed to some degree in the case of elderly subjects, there are cases in which urea ointment and zinc oxide ointment, etc. are used because of the moisture effects thereof.

Moreover, steroid preparations, anti-histamines and Crotamiton preparations, etc., have been widely used in the past as antipruritics.

Nevertheless, itching accompanying liver and renal disfunction and malignant tumors, metabolic disorders and senile pruritis, and pruritic skin diseases such as atopic dermatitis, eczema and urticaria, against which these antipruritics are unable to demonstrate antipruritic effects, are becoming a serious problem in the clinical setting.

As these diseases are frequently accompanied by serious itching, the particular condition may be exacerbated due to scratch to the skin resulting from that itching. As such, an antipruritic able to demonstrate adequate antipruritic effects has been long awaited. Furthermore, steroid preparations, antihistamines, and so on may cause problems due to adverse side effects, in certain cases.

## DISCLOSURE OF THE INVENTION

Accordingly, the object of the present is to eliminate the above-mentioned problems of the prior art by providing an antipruritic agent and antipruritic compound free of adverse side effects, acting directly on the itching itself, and being fast-acting.

In accordance with the present invention, there is provided an antipruritic comprising a zinc-amino acid complex.

In accordance with the present invention, there is also provided an antipruritic compound comprising an antipruritic agent comprised of a zinc-amino acid complex at a concentration of  $2.6 \times 10^{-3}$  -  $2.6 \times 10^{-1}$  M (molar concentration, moles/liter), and a pharmacologically acceptable carrier.

## BEST MODE OF CARRYING OUT THE INVENTION

As a result of intensive research by the inventors of the present invention, to achieve the above-mentioned object, it was discovered that an antipruritic agent having superior antipruritic properties and superior useability could be obtained by bonding zinc and an amino acid in a specific proportion, which led to the completion of the present invention.

Thus, it has been reported that itching receptors exist between the epidermis and dermis layers of the skin ("Modern Medicine", Vol. 16, No. 11, pp. 46 - 47, 1987, Asahi Shimbunsha), and that the skin contains a high content of zinc, containing roughly 20% of the total amount of zinc in the body, with particularly large amounts contained in the epidermis ("Zinc and Clinical Medicine", Asakura Shoten, pp. 20 - 21, p. 123, 1984), indicating that there is an intimate relationship between the skin and zinc metabolism. In addition, a characteristic systemic skin rash occurs in hereditary Acrodermatitis enteropathica, which is primarily caused by zinc deficiency, and a long-term implementation of high-calorie infusion (parental feeding). The cause of this in the former case is an insufficient absorption of zinc in the small intestine, while the cause in the latter case is the chelation of zinc in the body by amino acids and sugars contained in the infusion liquid resulting in transport and excretion of zinc outside the body. It has also been reported that these skin diseases are cured by a replacement of zinc ("Zinc and Clinical Medicine", Asakura Shoten, pp. 77 - 92, 1984). The inventors of the present invention have conducted the research by being aware of the relationship between zinc and itching. As a result of this research, it was found that the zinc-amino acid complex is effective in relieving itching.

zinc based on the results of research into zinc metabolism, a bound form of zinc and amino acid was used for the form in which zinc is supplied to the body.

The following provides a detailed description of the constitution of the present invention.

The zinc and amino acid, the main ingredients, are known substances and may be those which are commercially available.

The supply form of the zinc used in the present invention refers to zinc metal, its inorganic salts such as a sulfate, carbonate or nitrate thereof, as well as its organic salts such as an acetate or oxalate thereof.

In addition, the amino acid referred to in the present invention refers to neutral, acidic and basic and all other amino acids as well as their inorganic salts such as hydrochlorides thereof and their organic salts such as acetates thereof. Furthermore, neutral to acidic amino acids are particularly preferable, as they enhance the antipruritic effects.

In the antipruritic agent of the present invention, the preferable bonding mole ratio of zinc to amino acid is 1:2. When the bonding procedure is performed at a mole ratio of less than 1:2, adequate effects corresponding to the amount of zinc will not be obtained. In addition, when the amino acid is blended in at a mole ratio in excess of 1:2, no effects will be demonstrated due to the excess amount of amino acid.

The amount of zinc-amino acid complex blended into the antipruritic composition of the present invention is generally  $2.6 \times 10^{-3}$  -  $2.6 \times 10^{-1}$  M, preferably  $1.3 \times 10^{-2}$  -  $1.3 \times 10^{-1}$  M. When the amount of zinc-amino acid complex blended is too low, although the manufacturing of the drug is easy, the antipruritic effects are inferior, thus making this undesirable. Conversely, when the amount of zinc-amino acid complex blended is too high, it is necessary to use a large amount of glycerine and alcohol to dissolve the zinc-amino acid complex. This lowers the stability of the preparation and hinders the useability thereof, thus making this undesirable.

Furthermore, where the zinc-amino acid complex is less than  $1.3 \times 10^{-1}$  M, since it is soluble in water and physiological saline, it can be dissolved as is, thus allowing it to be used for external application or as an injection drug. Where, however, the zinc-amino acid complex exceeds  $1.3 \times 10^{-1}$  M, since it cannot be dissolved in water as is, it must be dissolved in glycerine, ethyl alcohol, glycol or water, etc.

The amount blended when blending glycerol into the antipruritic composition pertaining to the present invention is generally 5.0 - 60.0 wt%, preferably 10.0 - 50.0 wt%.

When the amount of glycerine blended is too low, it is not possible to dissolve the zinc-amino acid complex, thus making this undesirable. Conversely, when the amount of glycerine is too high, the useability of the composition is remarkably hindered, thus also making this undesirable.

A poly-glycerol such as di-glycerol can be used alone or in combination with glycerol, to dissolve the zinc-amino acid complex in place of glycerol.

The blended amount when blending ethyl alcohol into the antipruritic composition pertaining to the present invention is 3.0 - 50.0 wt%, preferably 5.0 - 40.0 wt%.

When the amount of ethyl alcohol blended is too low, it is not possible to dissolve the zinc, etc., thus making this undesirable.

Conversely, when the amount blended is too high, there is an increase in the degree of skin irritation, thus also making this undesirable.

Isopropyl alcohol or acetone, etc., also can be used to dissolve the zinc, etc., in place of ethyl alcohol, but ethyl alcohol is preferable in terms of solubility.

Examples of the glycol blended into the antipruritic composition pertaining to the present invention include propylene glycol, dipropylene glycol, 1,3-butylene glycol, hexylene glycol and polyethylene glycol. These glycols are blended in to function as assistants in dissolving the zinc-amino acid complex, and the amount blended is 0.5 - 30.0 wt%, preferably 5.0 - 20.0 wt%.

When the amount of glycol blended is too low, a large amount of glycerol and ethyl alcohol must be blended in order to dissolve the zinc-amino acid complex, and conversely, when the amount blended is too high, it will not be possible to dissolve the zinc-amino acid complex, thus making both cases undesirable.

In addition, the amount of water blended into the antipruritic compound pertaining to the present invention is generally 5.0 - 50.0 wt%, preferably 10.0 - 40.0 wt%.

As the zinc-amino acid complex most likely exists in the form of a complex, its solubility is extremely specific, and its stability is greatly affected by the pH thereof.

The antipruritic composition according to the present invention is maintained stable for a long time by adjusting same to a pH of 2.0 - 10.0, preferably 4.0 - 8.0.

In order to prepare an antipruritic composition in accordance with the present invention, antihistaminic, pain-relieving, buffer, polar oils, surface-active agents, water-soluble polymers, and other drugs can be blended as desired, in addition to the above-mentioned required ingredients.

The present invention is exemplified with reference to the following examples, but is not limited thereto.

dissolve a zinc-amino acid complex, etc., in excess of  $1.3 \times 10^{-1}$  M, where the amount of zinc-amino acid complex is less than  $1.3 \times 10^{-1}$  M, a combination of the above-mentioned ingredients is not always necessary.

In addition, the present invention is able to be applied in pharmaceutical or non-pharmaceutical products, as well as in cosmetics and drinks, and so on.

When using the antipruritic agent according to the present invention as a antipruritic composition for external application on the skin, the amount of zinc-amino acid complex is generally made to be  $2.6 \times 10^{-2}$  -  $2.6 \times 10^{-1}$  M, preferably  $1.3 \times 10^{-2}$  -  $1.3 \times 10^{-1}$  M.

Furthermore, when using the external use composition according to the present invention as a preparation for external application on the skin, those ingredients that are normally blended into ordinary external preparations for application on the skin, such as oils, water, surface activators, moisture retention agents, lower alcohols, thickeners, chelating agents, dyes, preservatives and perfumes, may be suitably blended.

In addition, external preparations for application on the skin broadly refer to those preparations used on the skin, and examples include external use medications such as ointments as well as facial cosmetic products such as a skin wash, milky lotions and cremes.

Moreover, the external use composition according to the present invention also can be used on the head. Examples of these applications include hair tonic, milky lotions for the scalp, hair liquid, hair shampoo, hair rinse, hair cream, and hair spray.

When used as a composition for external use on the head, oily ingredients, UV absorbers, preservatives, moisture retention agents, surface activators, perfumes, water, alcohol, thickeners, coloring agents, medicinal drugs, and so on can be blended in.

When using the antipruritic agent according to the present invention as an internal medicine or injection, those ingredients which are normally blended in general internal medicines and injections can be suitably blended in as necessary. Examples of such ingredients include vehicles such as cornstarch, lactose, glucose and crystal cellulose; binders such as starch, gelatin and acacia; decomposing agents such as agar, sodium carboxycellulose and sodium hydrogencarbonate; lubricating agents such as magnesium stearate and talc.; isotonic agents such as sodium chloride; buffers such as phosphate and borate; and, other additives, dissolving assistants, stabilizers and preservatives.

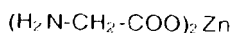
In addition, examples of the forms of these internal medicines include pharmaceuticals as well as powders, grains, granules, pills, tablets, capsules, internally consumed liquids and drinks in health foods, and beverages and so on.

## EXAMPLES

The following provides an explanation of suitable Examples of the present invention, but it is understood that the present invention is not limited to these Examples. Furthermore, unless specified otherwise, the zinc and amino acid amounts are indicated in molar concentrations.

First, the manufacturing process of the antipruritic agent according to the present invention will be explained.

### Example 1: Zinc-Glycine Complex



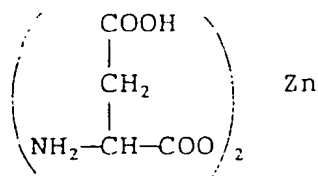
While stirring at 60°C after dissolving 1.65 g of glycine (commercially available product) in water, a solution of 2.37 g of zinc acetate dihydrate dissolved in 6 ml of water was dropwise added thereto. Stirring was performed for 30 minutes at the same temperature, after which the solution was allowed to stand overnight in a refrigerator. The precipitated solid was recovered by filtration and recrystallized with a mixture of ethanol and water to obtain 3.52 g of crystal.

M.P., >270°C

IR<sub>KBr</sub>: 3359, 1640 cm<sup>-1</sup>

Elementary analysis values, C <sub>8</sub> H <sub>14</sub> N <sub>2</sub> O <sub>6</sub> Zn·H <sub>2</sub> O			
Calculated values	C, 39.7%	H, 4.8%	N, 15.2%
Analysis values	C, 39.8%	H, 4.7%	N, 15.1%

## Example 2: Zinc-Aspartic Acid Complex



L-aspartic acid (2.00 g, 15.0 mmol) was added to an MeOH solution of NaOMe (prepared with Na: 0.69 g, MeOH: 50 ml) at 0°C and stirred. An MeOH solution (30 ml) of zinc acetate dihydrate (3.30 g) was then gradually dropwise added thereto at room temperature. After stirring for 2 hours at that same temperature, the precipitated crystal (in suspension) was recovered by filtration, washed with water, air dried, and then dried under a reduced pressure (5 mmHg, 80°C).

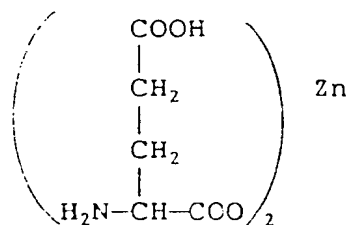
Yield: 1.65 g

M.P.: >270°C

IR<sub>KBr</sub>: 3300, 1640, 1630 cm<sup>-1</sup>

Elementary analysis values: C <sub>8</sub> H <sub>12</sub> H <sub>2</sub> O <sub>8</sub> Zn·H <sub>2</sub> O			
Calculated values:	C 27.64,	H 4.06,	N 8.06
Analytical values:	C 27.88,	H 4.10,	N 7.90

## Example 3: Zinc-Glutamic Acid Complex



L-glutamic acid (2.0 g, 13.6 mmol) was added to an MeOH solution of NaOMe (prepared with Na: 0.31 g, MeOH: 50 ml) at 0°C and stirred. An MeOH solution (30 ml) of zinc acetate dihydrate (1.49 g) was then slowly dropwise added thereto. After refluxing and stirring for 5 hours, the precipitated crystal (in suspension) was recovered by filtration, washed with water, air dried, and then dried under a reduced pressure (5 mmHg, 80°C).

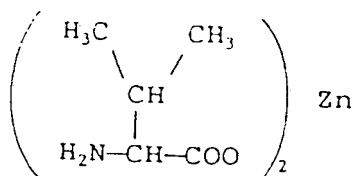
Yield: 1.40 g

M.P.: >270°C

IR<sub>KBr</sub>: 3400, 1645, 1640 cm<sup>-1</sup>

Elementary analysis values: C <sub>10</sub> H <sub>14</sub> N <sub>2</sub> O <sub>8</sub> Zn·2H <sub>2</sub> O			
Calculated values:	C 30.51,	H 5.12,	N 7.12
Analytical values:	C 30.79,	H 4.92,	N 7.35

## Example 4: Zinc-L-alanine Complex



10 L-valine (2.00 g, 17.1 mmol) was added to an MeOH solution of NaOMe (prepared with Na: 0.39 g, MeOH: 50 ml) at 0°C and stirred. An MeOH solution (30 ml) of zinc acetate dihydrate (1.90 g) was then slowly dropwise added thereto at room temperature. After stirring for 6 hours at that same temperature, the precipitated crystal (in suspension) recovered by filtration, washed with water, air dried, and then dried

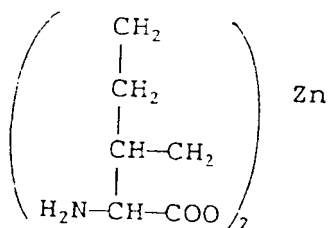
15 Yield: 0.40 g

M.P.: >270°C

IR<sub>KBr</sub>: 3400, 1640 cm<sup>-1</sup>

Elementary analysis values: C <sub>10</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub> Zn·3/2H <sub>2</sub> O			
Calculated values:	C 36.99,	H 7.14,	N 8.68
Analytical values:	C 37.13,	H 6.92,	N 8.46

## 25 Example 5: Zinc-Isoleucine Complex



30 L-isoleucine (2.00 g, 15.3 mmol) was added to an MeOH solution of NaOMe (prepared with Na: 0.35 g, MeOH: 50 ml) at 0°C and stirred. An MeOH solution (30 ml) of zinc acetate dihydrate (1.67 g) was then slowly dropwise added thereto at room temperature. After stirring for 2 hours at the same temperature, the solution was concentrated to half its original volume, followed by the addition of an equal volume of water. The precipitated crystal was recovered by filtration, air dried, and then dried under a reduced pressure (5 mmHg, 80°C).

40 Yield: 1.03 g

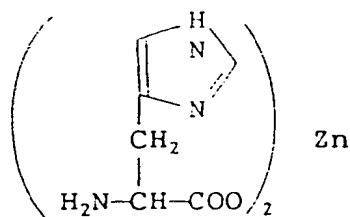
M.P.: >270°C

IR<sub>KBr</sub>: 3350, 1635 cm<sup>-1</sup>

Elementary analysis values: C <sub>12</sub> H <sub>24</sub> N <sub>2</sub> O <sub>4</sub> Zn·1/2H <sub>2</sub> O			
Calculated values:	C 43.06,	H 7.53,	N 8.37
Analytical values:	C 43.15,	H 7.42,	N 8.36

## 45 Example 6: Zinc-Histidine Complex





L-histidine (2.00 g, 12.8 mmol) was added to an MeOH solution of NaOMe (prepared with Na: 0.30 g, MeOH: 50 ml) at 0 °C and stirred. An MeOH solution (30 ml) of zinc acetate dihydrate (1.41 g) was then slowly dropwise added thereto at room temperature. After stirring for 3 hours, the precipitated crystal (in suspension) was recovered by filtration, washed with water, air dried, and then concentrated under a reduced pressure (5 mmHg, 80 °C).

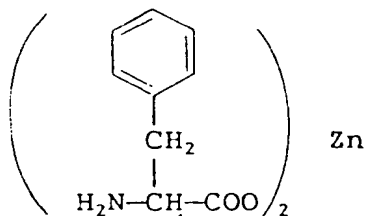
Yield: 0.40 g

M.P.: >285 °C

IR<sub>KBr</sub>: 3310, 1640 cm<sup>-1</sup>

Elementary analysis values: C <sub>12</sub> H <sub>13</sub> N <sub>3</sub> O <sub>4</sub> Zn·3/2H <sub>2</sub> O			
Calculated values:	C 35.97,	H 4.78,	N 20.97
Analytical values:	C 36.21,	H 4.58,	N 20.75

#### Example 7: Zinc-Phenylalanine Complex



L-phenylalanine (2.00 g, 12.1 mmol) was added to an MeOH solution of NaOMe (prepared with Na: 0.30 g, MeOH: 50 ml) at 0 °C and stirred. An MeOH solution (30 ml) of zinc acetate dihydrate (1.30 g) was then slowly dropwise added thereto at room temperature. After stirring for 3 hours, the precipitated crystal (in suspension) was recovered by filtration, washed with water, air dried, and then dried under a reduced pressure (5 mmHg, 80 °C).

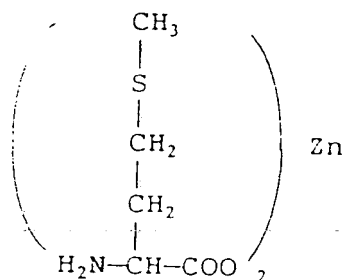
Yield: 2.06 g

M.P.: >270 °C

IR<sub>KBr</sub>: 3300, 1640 cm<sup>-1</sup>

Elementary analysis values: C <sub>13</sub> H <sub>13</sub> N <sub>2</sub> O <sub>4</sub> Zn·H <sub>2</sub> O			
Calculated values:	C 54.91,	H 5.12,	N 7.11
Analytical values:	C 54.73,	H 5.13,	N 7.00

#### Example 8: Zinc-Methionine Complex



L-methionine (2.00 g, 13.4 mmol) was added to an MeOH solution of NaOMe (prepared with Na: 0.30 g, MeOH: 50 ml) at 0°C and stirred. An MeOH solution (30 ml) of zinc acetate dihydrate (1.50 g) was then slowly dropwise added thereto at room temperature. After stirring for 3 hours, the precipitated crystal (in suspension) was recovered by filtration, washed with water, air dried, and then dried under a reduced pressure (5 mmHg, 80°C).

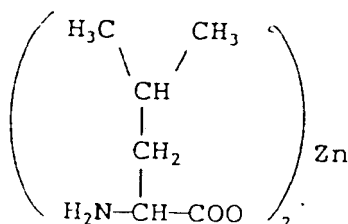
Yield: 2.13 g

M.P.: >270°C

IR<sub>(KBr)</sub>: 3310, 1640 cm<sup>-1</sup>

Elementary analysis values: C <sub>18</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub> Zn·3/2H <sub>2</sub> O			
Calculated values:	C 33.20,	H 5.57,	N 7.74
Analytical values:	C 33.12,	H 5.70,	N 7.66

#### Example 9: Zinc-Leucine Complex



L-Leucine (2.00 g, 15.3 mmol) was added to an MeOH solution of NaOMe (prepared with Na: 0.36 g, MeOH: 50 ml) at 0°C and stirred. An MeOH solution (30 ml) of zinc acetate dihydrate (1.67 g) was then slowly dropwise added thereto at room temperature. After stirring for 2 hours at that same temperature, the solution was concentrated to half its original volume, followed by the addition of an equal volume of water. The precipitated crystal was recovered by filtration, air dried, and then dried under a reduced pressure (5 mmHg, 80°C).

Yield: 2.00 g

M.P.: >270°C

IR<sub>(KBr)</sub>: 3350, 1635 cm<sup>-1</sup>

Elementary analysis values: C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>4</sub> Zn·1/2H <sub>2</sub> O			
Calculated values:	C 43.06,	H 4.53,	N 13.37
Analytical values:	C 43.29,	H 4.34,	N 13.29

The analytical values of the zinc leucine complex are in good agreement with the calculated values.

examined as follows.

#### Antipruritic Effects Test

Although the primary cause of itching is believed to be mainly related to histamine, there are many cases of itching which cannot be suppressed with anti-histamines, and these cases create serious problems in the clinical setting.

As such, prurigenic animal models were prepared in which itching cannot be suppressed by anti-histamines, by intracutaneously administering either bradykinin or kallikrein to guinea pigs, in order to confirm the antipruritic effects of the antipruritic agent according to the present invention.

#### (1) Antipruritic Effects Against Itching Induced by Bradykinin in Prurigenic Animals

The prurigenic substance, bradykinin, was intracutaneously administered to the flanks of healthy Hartley male guinea pigs to obtain the prurigenic animals.

The itching behavior was then evaluated following the evaluation standards indicated below, expressed in the form of itching activity.

Evaluation Method	Score
(1) Stressful behavior due to itching	1
When the animal demonstrated the following forms of behavior not normally observed:	
* Scratching of the face, ears, etc., with forepaw	
* Trembling of the body	
* Biting the floor or paws	
* Firmly standing on back legs	
(2) Scratching of the prurigenic site on the flank with the mouth or back legs	2
(3) Continuously repeating the behavior of (2) above three or more times	3

The above behavioral observations were performed simultaneously by three subjects or more for 20 minutes for each group of animals. The itching activity was scored and the mean value was then determined. These mean values were then indicated as antipruritic effects, taking the itching activity of a vehicle control group to be 100%.

The hair of the right flanks of healthy male guinea pigs (body weight: 450 - 600 g) was shaven using an electric shaver on the previous day, and thereafter the animals were grouped into groups of five animals each. Each of the groups were intracutaneously administered with 50 µg/0.05 ml of bradykinin into the right flank. After five minutes had elapsed, an externally applied vehicle was applied to one of the groups (control group) (composition: glycerine 40%, ethanol 25%, and water 35%). For the other groups, 0.1 ml of each sample containing the test substance at each concentration was externally applied to the site of intracutaneous administration of bradykinin. The itching behavior was then observed for 20 minutes, to determine the itching activity score.

A study was thus conducted regarding the type of anorectic and antipruritic effects based on the evaluation method described above. The results are indicated in Table I.

Table 1

Relationship Between Amino Acid and Itching Activity (n = 5)				
Amino Acid	Conc.	Zinc	Conc.	Itching Activity (%)
Vehicle control	-	-	-	100.0
Glycine	$2 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	67.5
Serine	$2 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	73.0
Cysteine	$2 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	70.8
Leucine	$2 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	82.3
Methionine	$2 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	70.5
Tyrosine	$2 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	70.5
Tryptophan	$2 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	72.6
Glutamic acid	$2 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	62.9
Histidine	$2 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	90.0
Arginine	$2 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	93.4
Lysine	$2 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	94.3

As is clear from Table 1, although a decrease in itching activity is observed for all zinc-amino acid complexes, particularly favorable antipruritic effects are observed for complexes of zinc and neutral to acidic amino acids.

The relationship between the bonding ratio of the zinc-amino acid complex and itching activity was examined as follows.

More specifically, the itching activity was examined by sequentially varying the amount of amino acid added with respect to a constant amount of zinc during the bonding reaction. The results are indicated in Table 2.

Table 2

Effects of the Antipruritic Agent of the Present Invention on Itching Caused by Bradykinin (n = 5)				
Amino Acid	Conc.	Zinc	Conc.	Itching Activity (%)
Vehicle control	-	-	-	100.0
Control	-	Zinc sulfate	$1 \times 10^{-2}$ M	98.0
Glycine	$0.5 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	96.7
Glycine	$1.0 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	94.0
Glycine	$1.5 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	93.5
Glycine	$2.0 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	68.3
Glycine	$4.0 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	71.1
Tryptophan	$0.5 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	96.8
Tryptophan	$1.0 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	95.7
Tryptophan	$1.5 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	95.0
Tryptophan	$2.0 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	67.9
Tryptophan	$4.0 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	69.0
Glutamic acid	$0.5 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	95.7
Glutamic acid	$1.0 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	92.1
Glutamic acid	$1.5 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	91.1
Glutamic acid	$2.0 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	61.8
Glutamic acid	$4.0 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	75.5

As is clear from Table 2 above, the zinc-amino acid complex demonstrates favorable antipruritic effects at a mole ratio of 1:2, but the antipruritic effects per unit amount of zinc decrease if the amount of zinc is increased beyond that ratio. Similarly, the antipruritic effects per unit amount of zinc do not improve when the amount of amino acid is also increased beyond that ratio.

Thus, it is suggested that zinc and amino acid form a special bound form at a mole ratio of 1:2 that demonstrates superior antipruritic effects.

This is believed to be probably due to the zinc and amino acid forming a complex in the ratio of 1:2.

## (2) Antipruritic Effects Against Itching Induced by Kallikrein in Prurigenic Animals

Kallikrein is another known physiological prurigenic substance which causes itching that cannot be suppressed with anti-histamines (International Journal of Dermatology, Vol. 14, pp. 456 - 484, 1975).

As such, prurigenic animals in which itching cannot be suppressed with anti-histamines were prepared by intracutaneously administering kallikrein to guinea pigs, in order to confirm the antipruritic effects of the antipruritic agent according to the present invention.

Furthermore, the evaluation method used was the same as that previously described.

The hair of the right flanks of healthy male guinea pigs (body weight 450 - 600 g) was shaven using an electric shaver on the previous day, and thereafter, the animals were grouped into groups of five animals each. Each of the groups were intracutaneously administered with 25 units/0.05 ml of kallikrein into the right flank. After five minutes had elapsed, an externally applied vehicle was applied to one of the groups (control group). For the other groups, 0.1 ml of each mixed compound of zinc and amino acid at each concentration was externally applied to the site of intracutaneous administration of kallikrein. The itching behavior was then observed for 20 minutes, to determine the itching activity levels.

The test was then carried out regarding the type of amino acid and antipruritic effects based on the observations of the itching behavior. The results are indicated in Table 3.

Table 3

Effects of the Antipruritic Agent of the Present Invention on Itching Caused by Kallikrein (n = 5)				
Amino Acid	Conc.	Zinc	Conc.	Itching Activity (%)
Vehicle control	-	-	-	100.0
Glycine	$2 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	72.3
Tryptophan	$2 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	78.0
Glutamic acid	$2 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	67.1
Histidine	$2 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	93.3
Arginine	$2 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	98.5

As is clear from Table 3 above, the antipruritic effects with respect to itching caused by kallikrein are excellent in the case of acidic to neutral amino acids such as glycine and glutamic acid.

Table 4

Effects of the Antipruritic Agent of the Present Invention on Itching Caused by Kallikrein (n = 5)				
Amino Acid	Conc.	Zinc	Conc.	Itching Activity (%)
Vehicle control	-	-	-	100.0
Control	-	Zinc sulfate	$1 \times 10^{-2}$ M	101.3
Glycine	$0.25 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	101.0
Glycine	$0.5 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	100.9
Glycine	$1.0 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	100.9
Glycine	$1.5 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	99.9
Glycine	$2.0 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	71.3
Glycine	$4.0 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	70.8
Glutamic acid	$0.25 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	99.6
Glutamic acid	$0.5 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	99.0
Glutamic acid	$1.0 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	98.8
Glutamic acid	$1.5 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	98.1
Glutamic acid	$2.0 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	67.5
Glutamic acid	$4.0 \times 10^{-2}$ M	Zinc sulfate	$1 \times 10^{-2}$ M	72.4

According to Table 4, excellent effects against itching caused by kallikrein were also observed for bound forms having a zinc to amino acid ratio of 1:2.

As indicated above, it was confirmed that the antipruritic agent of the present invention can be a new antipruritic agent having an effect against itching that cannot be suppressed with conventional anti-histamines and so on.

### (3) Effects due to Formation of a Complex

Next, the invention of the present invention contemplated the following experimental system in order to confirm whether the antipruritic effects of the present invention were due to the binding ratio of the zinc and amino acid, or due to the formation of a bound form (complex).

In Table 5, the results of the experiments are shown. The antipruritic effect was observed in the

concentration of  $1 \times 10^{-4}$  M. In the case of the zinc sulfate-amino acid mixture groups, the zinc sulfate was dissolved to a concentration of  $1 \times 10^{-4}$  M and the amino acid was dissolved to a concentration of  $2 \times 10^{-4}$  M. In the case of a zinc-amino acid complex, the complex was dissolved to a concentration of  $1 \times 10^{-4}$  M. In each case, water was used for the solvent. These solutions were then used as the test samples.

The bound substances (precipitates) formed in the above-mentioned Examples 1 - 9 are considered to be complexes, and stirring is required over an extended period of time in order to obtain the bound substances. Consequently, even if the zinc sulfate and amino acid were simply dissolved in solvent (zinc sulfate-amino acid mixture groups), the bound form (complex) essentially would not be formed.

Table 5

	n = 5	
	Itching Activity	
	Bradykinin	Kallikrein
Vehicle control group	100	100
Glutamic acid alone	101	102
Zinc sulfate-glutamic acid mixture group	87	90
Zinc-glutamic acid complex	65	67
Vehicle control group	100	100
Aspartic acid alone	101	101
Zinc sulfate-aspartic acid mixture group	91	91
Zinc-aspartic acid complex	70	69
Vehicle control group	100	100
Glycine alone	98	99
Zinc sulfate-glycine mixture group	88	92
Zinc-glycine complex	73	75

According to Table 5 above, the antipruritic agent according to the present invention possesses remarkable effects as a complex, and in addition, it is clear that it does not demonstrate antipruritic effects simply as a result of the coexistence of zinc and amino acid.

The following provides an explanation of the antipruritic composition which uses the antipruritic agent according to the present invention.

First, the composition of an external use antipruritic composition into which is blended the antipruritic agent according to the present invention, together with its pharmacological effects, are indicated in Table 6 below. Note, the blended amounts are indicated in wt%.

Table 6

		n=5			
		Example 10	Example 11	Comp. Example 1	Comp. Example 2
5	(1) Zinc-glycine complex	0.23	0.23	-	-
10	(2) Zinc sulfate <sup>*2</sup>	-	-	0.27	0.27
	(3) Glycine	-	5.0	-	0.08
15	(4) Glycerol		20.0		
	(5) Propylene glycol		10.0		
20	(6) Ethyl alcohol		5.0		
	(7) Hydroxypropyl cellulose		1.0		
25	(8) Methylparabenzene		0.05		
	(9) Purified water		Balance		
			Total 100.0%		
30	Itching Activity	Example 10	Example 11	Comp. Example 1	Comp. Example 2
	Bradykinin-induced itching	64	65	97	86
35	Kallikrein-induced itching	66	68	94	89

\*1 Monohydrate

\*2 Hexahydrate (each equivalent to roughly  $1 \times 10^{-2}$  M)

## Preparation Process

Ingredients (1) and (8) were added to ingredients (4) and (6), followed by heating to 40-50°C and stirring until dissolved. On the other hand, ingredient (5) was wetted in advance with ingredient (7) followed by the addition of ingredients (2), (3) and (9). After stirring until dissolved, the compound dissolved above was added gradually and stirred to obtain the desired preparation.

This antipruritic composition was stable even after long-term storage at temperatures over a range of -5 to 40°C.

According to Table 6 above, the antipruritic compositions according to Example 10 and Example 11 possess a superior antipruritic activity. In addition, as is clear from Example 11, the presence of oxazone, amino acid does not have an effect on antipruritic activity.

On the other hand, as described above, the zinc amino acid complex is first formed by stirring for an extended time in the presence of both zinc and amino acid. As indicated in Comparative Example 2, it is believed that simply blending zinc sulfate and glycine into the compound eventually does not contribute to formation of the zinc-glycine complex. This is due to the solubility of zinc sulfate and glycine in water.



As a result, it was determined that, in order for the composition to sufficiently demonstrate antipruritic effects, preferably the zinc-amino acid complex is formed in advance, after which said zinc-amino acid complex is added to each of the other ingredients.

#### Example 12: External Use Antipruritic Agent

(1) Zinc-serine complex	1.0 wt%
(2) Isopropyl alcohol	25.0 wt%
(3) Polyethylene glycol 300	20.0 wt%
(4) Glycerol	20.0 wt%
(5) Phosphate buffer	q.s.
(6) Purified water	Balance

#### Manufacturing Process

After adding ingredient (1) to ingredients (2) and (4), heating to a temperature of 40 - 50 °C and stirring until dissolved, ingredient (3) was added followed by stirring and mixing. On the other hand a solution resulting from dissolving ingredient (5) in ingredient (6) by stirring was added to the previously prepared liquid, followed by stirring, to obtain a stable preparation of pH = 5.6.

This antipruritic was stable even when stored for an extended time at -5 to 40 °C. Moreover, the antipruritic effects were extremely high, as indicated in the above-mentioned test of antipruritic properties.

#### Example 13: External Use Antipruritic Agent

(1) Zinc-cysteine complex	3.0 wt%
(2) Glycerol	40.0 wt%
(3) Ethyl alcohol	25.0 wt%
(4) 1,3-butylene glycol	10.0 wt%
(5) Isopropyl adipate	1.0 wt%
(6) Hydroxymethyl cellulose	0.3 wt%
(7) Purified water	Balance

#### Preparation Process

Ingredient (1) was added to ingredients (2) and (3), and after heating to a temperature of 40 - 50 °C and stirring until dissolved, ingredients (4) and (5) were sequentially added, followed by stirring and mixing. On the other hand, after dissolving ingredient (6) in ingredient (7), the composition prepared above was added gradually, and sufficiently stirred to obtain a stable preparation of pH = 5.50.

This antipruritic agent was stable even when stored for an extended time at -5 to 40 °C. Moreover, the antipruritic effects were extremely high, as indicated in the above-mentioned test of antipruritic properties.

#### Example 14: External Use Antipruritic Agent

(1) Zinc-leucine complex	5.0 wt%
(2) Glycerol	45.0 wt%
(3) Ethyl alcohol	30.0 wt%
(4) Dipropylene glycol	10.0 wt%
(5) Diethyl adipate	1.0 wt%
(6) Purified water	Balance

Preparation Process

To ingredient (1) was added ingredients (2) and (4), and after heating to a temperature of 40 - 50° C and stirring until dissolved, ingredients (4), (5) and (6) were added sequentially, followed by stirring, to obtain a stable preparation of pH = 5.2.

This antipruritic agent was stable even when stored for an extended time at -5 to 40° C. Moreover, the antipruritic effects were extremely high, as indicated in the above-mentioned test of antipruritic properties.

Example 15: Sunburn Cream

(1) Stearic acid	2.0 wt%
(2) Cetanol	5.0 wt%
(3) Hydrogenated oil	5.0 wt%
(4) Silicone KF96A-6-	5.0 wt%
(5) Squalane	10.0 wt%
(6) (POE) <sub>20</sub> stearyl ester	2.0 wt%
(7) Glyceryl monostearate	3.0 wt%
(8) Glycerol	10.0 wt%
(9) Zinc-methionine complex	0.5 wt%
(10) Antioxidant, preservative and perfume	q.s.
(11) Purified water	Balance

Preparation Process

Ingredients (1) through (7) and ingredient (10) were heated to dissolve at 70° C to prepare the oil phase.

On the other hand, ingredient (9) was added to ingredients (3) and (11). After heating and stirring until dissolved, the oil phase was gradually added, followed by processing with a homogenizer and cooling.

This suntan cream was stable when stored for an extended time at -5 to 40° C.

Example 16: Milky Lotion

(1) Cetanol	0.5 wt%
(2) Hydrogenated	1.0 wt%
(3) Stearic acid	1.0 wt%
(4) Squalane	3.0 wt%
(5) (POE) <sub>20</sub> mol sorbitan monolaurate	1.0 wt%
(6) Glyceryl monostearate	1.0 wt%
(7) Ethyl paraben	0.15 wt%
(8) Perfume	0.2 wt%
(9) Glycerol	10.0 wt%
(10) Dipropylene glycol	5.0 wt%
(11) Zinc-tyrosine complex	1.0 wt%
(12) Carboxyvinyl polymer 105	0.3 wt%
(13) Triethanol amine	1.0 wt%
(14) Purified water	Balance

Preparation Process

Ingredients (1) through (6) were heated at 70° C, and stirred until dissolved, to prepare the oil phase. In addition, ingredient (11) was dissolved in ingredients (9) and (10) and a portion of ingredient (14) to prepare the zinc-tyrosine complex phase. On the other hand, ingredient (12) was dissolved in the majority of ingredient (14) and heated to 70° C. To prepare the emulsion phase, the oil phase was gradually added to the

phase, followed by emulsion. After adding that in which ingredient (12) was dissolved in a portion of ingredient (14), the zinc-tyrosine complex phase was added, followed by processing with a homogenizer, stirring, and cooling to obtain the milky lotion.

This milky lotion was stable even when stored for an extended time at -5 to 40 °C.

#### Example 17: Skin Wash

(1) Glycerol	5.0 wt%
(2) Denatured ethyl alcohol	15.0 wt%
(3) (POE) <sub>60</sub> hydrogenated castor oil	1.0 wt%
(4) Zinc-tryptophan complex	0.3 wt%
(5) Perfume	q.s.
(6) Methyl paraben	0.2 wt%
(7) Allantoin	0.1 wt%
(8) Purified water	Balance

#### Preparation Process

Ingredients (1) through (6) were stirred until dissolved, at room temperature, to prepare the alcohol phase. In addition, after dissolving ingredient (7) in ingredient (8), the alcohol phase was gradually added while stirring, to form a uniform solution to obtain a skin wash.

This skin wash was stable when stored for an extended time at -5 to 40 °C, and moreover, possessed skin conditioning effects.

#### Example 18: Sunburn Ointment

(1) Zinc-glutamic acid complex	2.5 wt%
(2) Glycerol	35.0 wt%
(3) Polyethylene glycol (PEG-400)	25.0 wt%
(4) Polyethylene glycol (PEG-6000)	5.0 wt%
(5) Hydrogenated oil	12.0 wt%
(6) Stearic acid	2.0 wt%
(7) Isopropyl palmitate	2.0 wt%
(8) Glyceryl monostearate	3.0 wt%
(9) Methyl paraben	0.2 wt%
(10) Potassium hydroxide	0.1 wt%
(11) Purified water	13.2 wt%

#### Preparation Process

Ingredients (1) through (4) and a portion of ingredient (11) were added and stirred at 70 °C until dissolved, to prepare the zinc-glutamic acid complex phase. On the other hand, ingredients (5) through (9) were heated to 70 °C to prepare the oil phase. Ingredient (10) was added to ingredient (11), followed by heating until dissolved, to which was then added the above oil phase. Finally, the previously prepared zinc-glutamic acid complex phase was added. After creating a uniform mixture with a homogenizer, the mixture was stirred and cooled to obtain the sunburn ointment.

This ointment was stable when stored for an extended time at -5 to 40 °C.

#### Example 19: Emulsion Ointment

(1) Diglycerol isostearate	2.0 wt%
(2) Water-swelling clay mineral (hectrite) <sup>11</sup>	1.5 wt%
(3) Benzyldimethylstearylammmonium chloride	0.5 wt%
(4) Dimethyl polysiloxane	5.0 wt%
(5) Liquid paraffin	18.8 wt%
(6) Microcrystalline wax	2.0 wt%
(7) Ethyl paraben	0.2 wt%
(8) Deionized water	10.0 wt%
(9) Glycerol	48.0 wt%
(10) Propylene glycol	10.0 wt%
(11) Zinc-histidine complex	2.0 wt%

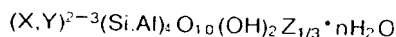
### Preparation Process

After sufficiently allowing ingredient (2) to swell inside ingredient (8), it was dispersed in a solution in which ingredients (9), (10) and (11) were heated and dissolved in advance, to form the aqueous phase.

On the other hand, oil-soluble ingredients (1) and (3) through (7) were mixed and dissolved at roughly 70 °C, to obtain the oil phase. When the above aqueous phase was gradually added while stirring the oil phase with a stirring rod, an emulsified dispersion system was obtained. This was then cooled to room temperature to obtain the desired emulsion ointment.

This emulsion ointment was stable when stored for an extended time at -5 to 40 °C, and possessed skin conditioning effects.

Furthermore, the water-swelling clay mineral<sup>11</sup> used in this Example is a type of colloidal hydrate aluminum silicate having a three layer structure, and is generally expressed with the general formula indicated below:



where,

X = Al, Fe<sup>III</sup>, Mn<sup>III</sup>, Cr<sup>III</sup>

Y = Mg, Fe, Ni<sup>II</sup>, Zn, Li

Z = K, Na, Ca

More specifically, this is comprised of natural or synthetic (in this case, the (OH) group in the formula is substituted with fluorine) members of the montmorillonite group such as montmorillonite, saponite and hectrite.

### Example 20: Hair Tonic

(1) Denatured ethyl alcohol	65.0 wt%
(2) Propylene glycol	5.0 wt%
(3) Glycerol	5.0 wt%
(4) Zinc-arginine complex	0.5 wt%
(5) Perfume	q.s.
(6) (POF) <sub>50</sub> hydrogenated castor oil	1.0 wt%
(7) Hinokitiol	0.01 wt%
(8) Vitamin E acetate	0.1 wt%
(9) Purified water	Balance

### Manufacturing Process

After heating and dissolving ingredient (4) in ingredients (1), (2) and (3), ingredients (6), (7) and (8) were added followed by stirring until dissolved. Then, ingredient (5) was added gradually to the mixture, and the mixture was cooled.

This hair tonic was stable when stored for an extended time at -5 to 40 °C.

Example 21: Tablet

100 mg of lactose, 30 mg of cornstarch, 80 mg of talc and 2 mg of magnesium stearate were added and mixed with 100 mg of zinc-lysine complex and formed into tablets.

In the case of an enteric coated preparation, the above-mentioned tablet was coated with an enteric coating of hydroxypropylmethyl cellulose phthalate to obtain the enteric coated tablet.

This tablet was stable when stored for an extended time at -5 to 40 °C.

Example 22: Capsule

150 mg of lactose, 100 mg of cornstarch and 1 mg of light-gravity silicic anhydride were added and mixed with 50 mg of zinc-glycine complex and filled into a No. 2 gelatin hard capsule. In the case of an enteric coated capsule, the above-mentioned capsule was coated with an enteric coating of hydroxypropylmethyl cellulose phthalate to obtain the enteric coated capsule. This capsule was stable when stored for an extended time at -5 to 40 °C.

Example 23: Injection Preparation

Zinc-serine complex was dissolved in Japanese Pharmacopoeia physiological saline in the proportion of 10 mg of complex to 10 ml of saline. This solution was then filtered through a sterile membrane filter. After dividing the filtrate among sterilized ampules, the ampules were sealed.

This injection preparation was stable when stored for an extended time at -5 to 40 °C.

Industrial Applicability

According to the antipruritic agent or antipruritic composition of the present invention containing a zinc-amino acid complex, it is able to demonstrate superior antipruritic effects even with respect to itching for which sufficient antipruritic effects were unable to be obtained with conventional antipruritic agents or antipruritic compositions.

**Claims**

1. An antipruritic agent comprising a zinc-amino acid complex.
2. An antipruritic agent as claimed in Claim 1, wherein the bonding mole ratio of zinc-amino acid of the above-mentioned zinc-amino acid complex is 1:2.
3. An antipruritic agent as claimed in Claim 1 or 2, wherein the amino acid is at least one compound selected from the group consisting of acidic amino acids and neutral amino acids.
4. An antipruritic compositions comprising the antipruritic agent described in any one of Claims 1 to 3 at a concentration of  $2.6 \times 10^{-3}$  to  $2.6 \times 10^{-1}$  M, and a pharmacologically acceptable carrier.

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/JP91/01703

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) \*

According to International Patent Classification (IPC) or to both National Classification and IPC  
Int. Cl<sup>5</sup> A61K31/315, A61K31/40, A61K31/415

## II. FIELDS SEARCHED

Minimum Documentation Searched ?

Classification System

Classification Symbols

IPC

A61K31/315, A61K31/40, A61K31/415  
A61K31/195, A61K33/30, A61K7/00, A61K7/06

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are included in the Fields Searched \*

## III. DOCUMENTS CONSIDERED TO BE RELEVANT \*

Category *	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
A	JP, A, 02-196791 (Laboratoire Pharmaceutic Rochboz), August 3, 1990 (03. 08. 90) & EP, A, 368758 & FR, A, 2638748 & CA, A, 2001889	1-4
A	JP, A, 62-36314 (Ed. Gaistorich Zeene AG. für chemisch Industry), February 17, 1987 (17. 02. 87) & EP, A, 206692	1-4
A	JP, A, 57-82318 (Doron Ganfinkel), May 22, 1982 (22. 05. 82) & EP, A, 48473	1-4
A	JP, A, 60-174707 (Kanebo, Ltd.), September 9, 1985 (09. 09. 85), (Family: none)	1-4
A	JP, A, 55-45611 (Max Rosenberg), March 31, 1980 (31. 03. 80) & US, A, 4107331 & DE, A, 2844814 & FR, A, 2437833	1-4

\* Special categories of cited documents: <sup>14</sup>

"A" document defining the general state of the art which is not  
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"E" earlier document but published on or after the international  
filing date

"L" document which may throw doubts on priority claim(s) or  
which is cited to establish the publication date of another  
citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or  
other means

"P" document published prior to the international filing date but  
later than the priority date claimed

"T" later document published after the international filing date or  
priority date and not in conflict with the application but cited to  
understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot  
be considered novel or cannot be considered to involve an  
inventive step

"Y" document of particular relevance: the claimed invention cannot  
be considered to involve an inventive step when the document  
is combined with one or more other such documents, such  
combination being obvious to a person skilled in the art

"&" document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search

Date of Mailing of this International Search Report

February 16, 1992 (10. 02. 92)

March 10, 1992 (10. 03. 92)

International Searching Authority

Signature of Authorized Officer

Japanese Patent Office